

principal investigator for the team. His collaborators were Jean-Pierre Kinet, a professor of pathology at Harvard Medical School who first cloned the gene for the IgE receptor in 1986, and Scott Garman, a postdoctoral fellow in the Northwestern Department of Biochemistry, Molecular Biology, and Cell Biology.

About 50 million people in the United States have some form of allergy. Many allergies, such as hay fever and eczema, are more inconvenient than life-threatening, but some allergic responses, such as anaphylaxis, can result in death. Allergies are also strongly suspected of playing a role in asthma. According to the National Institute of Allergy and Infectious Diseases, 90% of asthmatic children and 50% of asthmatic adults also have allergies. According to the Centers for Disease Control and Prevention, asthma accounts for almost 500,000 hospitalizations each year and is the foremost reason that children miss school. And the problem is growing—asthma prevalence in the United States is expected to rise by 5% each year.

Allergic responses are mediated by IgE, which is one of five classes of antibodies. As IgE circulates through the blood and the lymph, it binds to receptors found on the surface of mast cells (a type of white blood cell). There, IgE acts as an antenna, patrolling its airspace for allergens. When an antibody picks up the signal of a nearby allergen, the mast cell responds by releasing histamine and other powerful chemicals that cause an inflammatory response in surrounding tissues.

Mast cells are found throughout the body but are most highly concentrated in tissues that are exposed to the outside world, such as the skin and nasal and lung linings. So when an allergic response occurs, those tissues are most likely to be affected, resulting in the rashes, welts, runny noses, and watery eyes traditionally associated with allergies.

The IgE receptor had previously defied imaging because it has a heterogeneous sugar coating that solubilizes the receptor and prevents it from crystallizing into a structure that can be examined through X-ray diffraction. To counteract this problem, the scientists expressed the human IgE receptor gene in cultured insect cells from the cabbage looper and the fall armyworm, which attach fewer sugars to the molecule. Next, they applied a technique called multiple isomorphous replacement, in which IgE receptor crystals were soaked in one of two solutions containing either gold or platinum. The large, heavy atoms of the metals were absorbed into the crystals, adding mass in the form of electrons

Toxic Toys

The controversy about the safety of children's toys continues to play out in the scientific community and the media. Not only are there concerns about pesticides accumulating on toys, there is also fear that some of the chemicals used to manufacture toys may be posing risks to children's health. Phthalates, chemicals that are added to polyvinyl chloride (PVC) polymers to create flexible plastics, are receiving most of the attention. Phthalates are used in products such as shower curtains, raincoats, balls, squeeze toys, and medical devices such as tubing and IV bags.

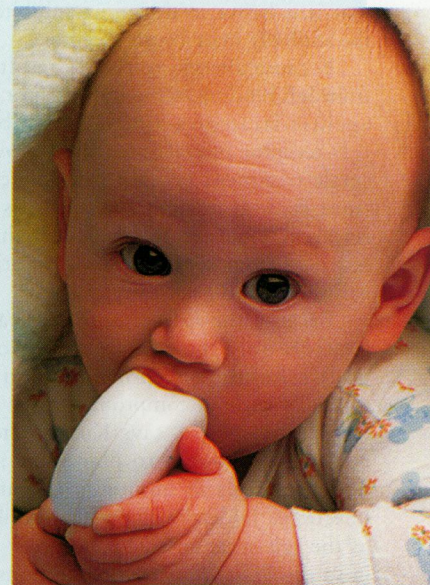
Studies in the 1960s detected phthalates in biological samples, indicating that the chemicals leach out of PVC plastics. The NIEHS and the National Toxicology Program (NTP) began studying phthalates following a 1970s discovery that blood stored in PVC plastic bags that was used for transfusions contained measurable concentrations of phthalates, and that the chemicals were found in the organs of humans who had received transfusions.

Initially, the most widely studied phthalate was the commonly used di(2-ethylhexyl) phthalate (DEHP). In 1982, NTP studies showed that DEHP induced a strong liver tumor response in rats and mice. Since the 1980s, the NIEHS and the NTP have conducted carcinogenicity studies on four other phthalates, which were not found to cause cancer. They have also conducted reproductive and developmental toxicity testing on 12 phthalates and found that toxicity varies widely among the class.

In response to the finding of DEHP's carcinogenicity and to additional findings suggesting that DEHP may be toxic to the reproductive system, U.S. toy makers agreed in 1986 to limit the concentration of the chemical in teething rings, pacifiers, and squeeze toys to 3%. Many toy makers began substituting diisononyl phthalate (DINP) for DEHP in these products. However, the environmental advocacy group Greenpeace released a study in December 1998 claiming that tests it had conducted found DEHP levels of 6–44% by weight in a variety of other children's products that are likely to be placed in the child's mouth, such as plastic bibs. In the controversy that continues to rage about the risks posed to children by phthalates in toys, a major point of contention is the amount of phthalates that leaches out of toys and into children's mouths.

In the first study to examine the amount of a phthalate that migrates out of children's products, the U.S. Consumer Product Safety Commission examined 31 different products containing DINP. At high doses in industry-sponsored studies, DINP has been linked with liver tumors and has been shown to cause damage to the liver, kidney, and other organs in mice and rats. The results, published in December 1998, also indicate that the amount of DINP ingested by children is well below harmful levels. The commission concluded that few, if any, children are at risk for toy-related DINP exposures and therefore did not recommend a ban on products containing the chemical. However, at the commission's request, 90% of manufacturers agreed to remove phthalates from soft rattles and teething rings by early 1999. According to Greenpeace, Austria, Denmark, Finland, Greece, Norway, and Sweden have also banned or taken steps to ban phthalates in toys for children under the age of three years due to fears about infant exposure.

The Clinton administration has asked the NIEHS and the NTP to continue studying phthalates. The new NTP Center for the Evaluation of Risks to Human Reproduction announced in April that its first review will look at reproductive risks to plastics workers and consumers from seven phthalates, including DEHP and DINP, that are widely used in consumer products.



to the receptor at key points and making it possible to calculate its image. According to Jardetzky, by comparing data that correspond to the receptor by itself to another set of data that reflects the changes effected by the binding of one of these heavy metals to the receptor, the researchers can calculate the structure of the receptor.

The researchers then used the very high intensity X rays of the Advanced Photon Source at Argonne National Laboratory in Illinois to scrutinize the IgE crystals. The Advanced Photon Source is a synchrotron, which uses magnetic fields to maintain

charged particles in an orbit. The orbiting particles give off energy in the form of X rays. Special detectors measure the X rays as they bounce off the crystal being analyzed, and computers convert the data into an image of the crystal.

The researchers found that the receptor has an inverted "V" shape. At one end of the V is a spike that attaches the receptor to the cell membrane. The IgE antibody binds at the upward-pointing elbow of the V shape. Jardetzky and colleagues are currently investigating several potential inhibitors and are working on capturing an image of